



U.S. Food and Drug Administration

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# **Good Clinical Practice (GCP) Update**

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# Overview

- I. Challenges in Today's Clinical Trials Environment
- II. Human Subject Protection (HSP)/Good Clinical Practice (GCP)/Bioresearch Monitoring (BIMO) Initiatives
- III. Accomplishments
- IV. What's Next?
- V. FY '10 BIMO Inspection Data

# I. Challenges in Today's Clinical Trials Environment

- Trials are complex, involve novel therapies or products
- More trials conducted outside of academic centers
- More large, multisite trials
- More overseas/non-US trials/sites
- More trials involving vulnerable populations
- Ever-changing pool of investigators
- Outsourcing/delegation of responsibilities

# I. Challenges in Today's Clinical Trials Environment

- Increase in IRBs' responsibilities
  - Ethical review of research
  - Management of conflicts of interest
  - Privacy
  - Risk management
- IRB Stresses/Burdens
  - Institutional pressures
  - Limited resources

# **I. Challenges in Today's Clinical Trials Environment**

## **Patient Interests in Clinical Trials**

- Want more information about and access to investigational therapies
- Do not want limits on clinical trial participation, but
- Concerned about adequate protection for study subjects

# I. Challenges in Today's Clinical Trials Environment

OIG/GAO/Congress/Media/Public Interest:

- Investigators' financial ties to sponsors and products
- Adequacy of FDA oversight of CI responsibilities and trial conduct
- Adequacy of IRB oversight
- Safety of trial participants
- Adverse events and clinical trial results

# I. OIG Investigation – FDA's Oversight of CI Financial Disclosure Information (2009)

- Reviewed types of financial disclosures, sponsor monitoring of arrangements, and extent to which FDA oversees:
  - Financial information submitted to agency
  - Inspection of CI and sponsor records
- Recommendations to FDA:
  - Greater accountability of CIs and sponsors
  - Additional guidance/training for FDA review staff
  - Follow-up during CI and sponsor inspections

# I. GAO Investigation – FDA’s DQ/Debarment Processes (2009)

- Comprehensive review of 52 DQs, 18 Debarments
- GAO noted:
  - FDA previously lacked procedures/timeframes
  - Recently revamped both processes to include responsible parties, timeframes, training, database
- Recommendations to FDA:
  - Pursue debarment authority for medical devices
  - Amend regulations to ensure that disqualified CIs may not conduct clinical trials for any FDA-regulated product
  - Aggressive monitoring and enhanced transparency of pending cases

# I. Congressional Hearing

(March 2009)

GAO Sting Operation -- *“Human Subjects Research: Undercover Tests Show the Institutional Review Board System is Vulnerable to Unethical Manipulation”*

- Focus on commercial IRBs
- GAO presented fake device/protocol
  - Submitted to 3 IRBs
  - Coast IRB approved study
  - Coast, OHRP, and FDA testified before the Energy and Commerce Committee’s Subcommittee on Oversight and Investigations

# I. Congressional Hearing (Cont.)

- After the Hearing:
  - FDA issued Warning Letter to Coast IRB
  - FDA inspected Coast
  - Coast IRB ceased operations
  - Active studies transferred to other IRBs
- Lessons Learned - FDA determined IRBs and sponsors need clarification
  - When an IRB goes out of business or study is terminated prematurely
  - Understanding/Applying Regulations (e.g., Subpart D, device risk determinations)

## II. HSP/GCP/BIMO Initiatives

### **HSP/BIMO Modernization – 2006 Critical Path initiative announcement**

- External outreach, including PhRMA, AdvaMed
- Formation of HSP/BIMO Council (2006)
  - Comprised of senior scientists and managers; chaired by the director of the Office of Good Clinical Practice (OGCP)
  - Variety of scientific/regulatory/legal backgrounds
  - Guiding body and decision-making group on activities and policy development related to modernization of HSP and BIMO regulations
- Development of yearly GCP workplan with priority documents identified

## **II. HSP/GCP/BIMO Initiatives**

### **Office of Good Clinical Practice (OGCP)**

- Coordinates across FDA's Centers/ORAs to help BIMO Program meet its goals to:
  - Protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
  - Determine the accuracy and reliability of clinical trial data submitted to FDA; and
  - Assess compliance with FDA's regulations governing the conduct of clinical trials.

# II. HSP/GCP/BIMO Initiatives

## OGCP Activities

- Guidance and regulation development, with Centers and ORA
- Chair GCP BIMO Roundtable/lead WGs
- HSP coordination with other government agencies (OHRP, VA, etc)
- Internal training of reviewers, BIMO field & HQ staff; external outreach to stakeholders
- International GCP capacity-building and standards harmonization (ICH, ISO)
- Agency GCP website/queries/outreach

## **II. HSP/GCP/BIMO Initiatives**

### **Clinical Trials Transformation Initiative (CTTI)\***

- Public-private partnership between Duke University and FDA
- Aim: To improve the quality and efficiency of clinical trials
- Comprised of over 50 organizations, including government agencies, industry representatives, patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties

\* CTTI information courtesy of CDER/Office of Medical Policy

## II. HSP/GCP/BIMO Initiatives

### CTTI

- Created to address a crisis in US clinical research, however:
  - Trials and issues are global
- Seeks to identify:
  - Discordant approaches to trial planning, conduct, and oversight that may benefit from harmonization
  - Process improvements and best practices that can be applied globally
- Includes international collaboration

## II. HSP/GCP/BIMO Initiatives

### What Makes CTTI Unique?

- Conducts projects that will generate evidence to inform regulators and other stakeholders about strategies and practices that will improve the clinical research enterprise
- Broad array of stakeholders and energetic involvement of CTTI members in project development and implementation
- FDA and other regulators are active participants in the effort
- Committed to fostering change in how clinical trials are conducted based on results of CTTI projects

# II. HSP/GCP/BIMO Initiatives

## CTTI Projects -1

- Effective and Efficient Monitoring
  - Goal: to identify best practices and develop sensible criteria to help sponsors choose the most appropriate monitoring methods for a trial
- Improving Unexpected SAE Reporting to Investigators
  - Goal: to generate empirical evidence about the current U.S. system for reporting serious adverse events (SAEs) to investigators under an IND application, and to identify potential system modifications to more efficiently and effectively inform investigators of such events

# II. HSP/GCP/BIMO Initiatives

## CTTI Projects – 2

- ClinicalTrials.gov
  - Goal: to derive and maintain, via quarterly updates, a publicly accessible, user-friendly analysis dataset of the ClinicalTrials.gov content, accompanied by a data dictionary
- Site Metrics
  - Goal: to identify core data elements that should be collected by all clinical trial sites to enable measurement and improvement of important timeframes for study start-up

## **II. HSP/GCP/BIMO Initiatives**

### **CTTI Projects – 3**

- Central IRB Project
  - Goal: To identify potential solutions to address barriers to the adoption of central IRBs for multicenter clinical trials

## II. HSP/GCP/BIMO Initiatives

### CTTI – Future Directions

- **Workshops on Quality-by-design (QbD) in clinical trials**
  - **Proposal:** Conduct a meeting to share “learnings” across industry regarding the application of QbD and integrated quality management planning in the clinical trial setting
  - **Goal:** Provide opportunity for dialogue among relevant stakeholders, including industry and regulators, to accelerate adoption of QbD and integrated quality management planning in the clinical trial setting.

## **II. HSP/GCP/BIMO Initiatives**

### **CTTI Collaborations**

- FDA Clinical Investigator Training Course
- Standards for Collecting Information about Cardiovascular Events – collaborative pilot project to develop standard definitions and data collection methods for cardiovascular events in clinical trials

# III. Accomplishments

## Related to BIMO

- Development of BIMO program goals and metrics (for future evaluation of the program)
- Enhanced enforcement
  - Ensures that data upon which the agency relies are scientifically valid, ethical, and accurate
  - Protects subjects by limiting activity of non-compliant clinical investigators/sponsors
  - Increases transparency so IRBs and sponsors are informed about problematic CIs

# III. Accomplishments

## Related to BIMO

- “Early Intervention Program”
  - More inspections while trials are on-going
  - Goal = prompt correction of problems identified
    - Minimize risks to subjects
    - Preserve the integrity of the data
- “Risk-based” Site Selection
  - Examples: studies involving pediatric or vulnerable subjects; no or problematic inspection history; high risk studies; novel products

# III. Accomplishments

## Related to BIMO

- Updated CI CPGM (Dec. '08)\*
  - Enhanced section regarding communication between HQ and DO
  - Defined inspection classification criteria, especially for WL & NIDPOE
  - Defined “repeated” and “deliberate”
  - Added collection of CI financial disclosure information

\* All additions = OIG recommendations

# III. Accomplishments

## Related to BIMO

- Updated Sponsor/Contract Research Organizations (CROs)/Monitors CPGM (March 11, 2011)
  - Used CI CPGM formatting – working towards consistency among BIMO CPGMs
  - Content and emphasis modified to reflect regulatory and policy changes since February 2001 (last CPGM update) – e.g., inspection of financial disclosure records, review of OUS study documentation, new IND safety reporting rules, expansion of electronic records inspection guidance, ClinicalTrials.gov
  - Added/updated references for new regulations and guidance documents
  - Verified accuracy of all links to references

# III. Accomplishments

## Related to BIMO

- Revamped CI Disqualification Process
- Developed Regulatory Procedures Manual (RPM) section with timeframes for the DQ process (issued Jan. '09)
  - Includes timeframes for the Centers and OCC
  - Covers issuance of the NIDPOE, follow-up correspondence and/or meetings, and issuance of an NOOH when needed

# III. Accomplishments

## Related to BIMO

- Revised FDA Information Sheet on the CI DQ process (issued May '10)
- Revised FDA Information Sheet on CI Inspections (issued June '10)
- Draft guidance regarding determination of when an IND is required (issued Oct. 14, 2010)

# III. Accomplishments

## Related to BIMO

- Proposed Rule regarding CI DQ (issued April 13, 2011)
- Draft Guidance on CI financial disclosure – (revision) (issued May 24, 2011)

# III. Accomplishments

## Related to Subject Safety

- Clinical Trial Registration Requirements  
<http://www.clinicaltrials.gov/>
  - Comprehensive listing of clinical trials
  - Assists patients in locating trials for their disease or condition
  - Transparency of trial results, including AEs
- Final rule requiring an additional element in informed consent documents when trials are registered on ClinicalTrials.gov (issued Jan. 4, 2011; effective March 7, 2011; compliance date March 7, 2012)

# **III. Accomplishments**

## **Related to Subject Safety**

- Final guidance on AE Reporting to IRBs (issued Jan. '09)
- Final Rule on Expanded Access to Investigational Drugs for Treatment Use (Aug.' 09)
- Final guidance on Investigator Responsibilities (issued Oct. '09)

# III. Accomplishments

## Related to Subject Safety

- Final rule on IND Safety Reporting, including BEQ studies (issued Sept. '10)
- Draft guidance on IND and BEQ Safety Reporting (issued Sept. '10)
- Final guidance on 50.24 studies (issued April 4, 2011)

# III. Accomplishments

## Related to IRBs

- Local/Centralized Review Alternatives (issued March '06)
- AE Reporting to IRBs (issued Jan. '09)
- IRB Registration (Final Rule issued Jan. '09; effective July 14, 2009, with compliance date of September 14, 2009)
- FAQs regarding IRB Registration (issued July '09)

# **III. Accomplishments**

## **Related to Data Quality and Integrity**

- FDA co-sponsored two public workshops
  - Quality in Clinical Investigations
  - Alternative Monitoring Approaches in Clinical Trials
- CTTI (MOU – Nov '07)

# **III. Accomplishments**

## **Related to Data Quality and Integrity**

- Proposed Rule – Reporting Information Regarding Falsification of Data (issued Feb.'10)
- Draft guidance on electronic source data in clinical trials (issued Jan.'11)

# III. Accomplishments

## Related to international clinical trials

- Final rule on 312.120 issued; Effective Oct. '08
- FAQ on Form 1572 (final guidance issue May '10)
- Continued capacity building
  - Inspection workshops in Thailand ('08 and '09); India ('08, '09 and '10); China ('10 and '11), Russia ('10 and '11), Botswana ('10), and South Africa ('11)

# III. Accomplishments

## Collaboration with OHRP

- Harmonization efforts to reduce burdens on all parties to the extent possible, given different statutory responsibilities and mandates
  - IRB Registration requirements
  - Guidance – IRB continuing review; retention of data when subjects withdraw; exculpatory language
  - Educational programs

# IV. What's next?

## Related to BIMO

- Revision of the IRB CPGM (in clearance)
- Proposed changes to regulations to include all parties involved with clinical trials (drafting –CDER has the lead)
- Draft guidance on monitoring clinical trials (in clearance)

# IV. What's next?

## Related to Subject Safety

- Informed Consent guidance (draft in clearance)
- Guidance on Responsible Inclusion of Pregnant Women in Clinical Trials (final in clearance)
- Guidance on the additional informed consent element related to ClinicalTrials.gov
- Protection of Vulnerable Populations
  - Pediatric - finalization of 21 CFR 50, Subpart D; Decisionally-Impaired; Emergency Research

# IV. What's next?

## Related to subject safety and IRBs

- NPRM to modify HSP regulations
- ANPRM issued July 25, 2011 = *Human Subject Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators* (HSP ANPRM)
- Specifically addresses proposed modifications to the Common Rule – 45 CFR Part 46; FDA HSP regulations discussed as well (21 CFR Parts 50 and 56)

# IV. What's next?

## Related to subject safety and IRBs (cont.)

**HSP ANPRM** includes seven (7) proposals:

1. Revising the existing risk-based framework to more accurately calibrate the level of review to the level of risk.
2. Using a single Institutional Review Board review for all domestic sites of multi-site studies.
3. Updating the forms and processes used for informed consent.
4. Establishing mandatory data security and information protection standards for all studies involving identifiable or potentially identifiable data.

# IV. What's next?

## HSP ANPRM proposals (cont.):

5. Implementing a systematic approach to the collection and analysis of data on unanticipated problems and adverse events across all trials to harmonize the complicated array of definitions and reporting requirements, and to make the collection of data more efficient.
6. Extending federal regulatory protections to apply to all research conducted at U.S. institutions receiving funding from the Common Rule agencies.
7. Providing uniform guidance on federal regulations

# IV. What's next?

## Related to IRBs

- IRB Continuing Review (draft issued for comment Jan. '10; final in clearance)
- Draft guidance on considerations for transferring study oversight to a new IRB (in clearance)

## IV. What's next?

### Related to international clinical trials

- Proposed rule to revise device regulations regarding acceptance of OUS studies for review (in clearance)
- Continued capacity building
  - Inspection workshop in the Middle East (Saudi Arabia) ('12)

# IV. What's next?

## Continued Collaboration with OHRP

- Addressing SACHRP's recommendations
  - Studies involving specimens
  - Minor changes to approved research
- Continued participation in OHRP's educational programs –  
<http://www.hhs.gov/ohrp/education/conferences/index.html>

# **V. FY'010 Inspectional Data**

# BIMO Inspections Completed FY 2010

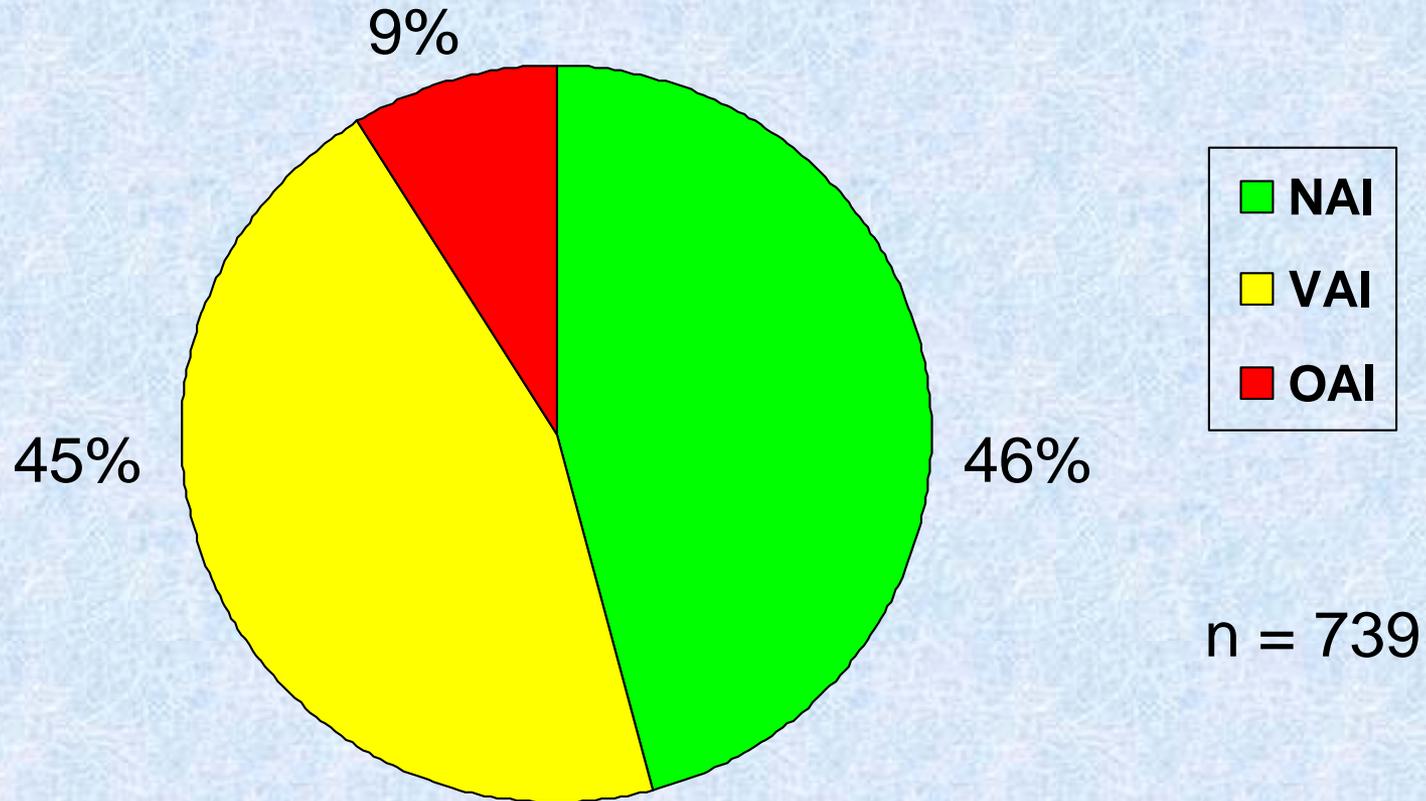
<u>Center</u>	<u>CI</u>	<u>IRB</u>	<u>Spon/Mon</u>	<u>GLP</u>	<u>Total</u>
<b>CBER</b>	75	25	14	11	125
<b>CDER*</b>	393	97	61	35	586
<b>CDRH</b>	218	81	80	7	386
<b>CFSAN**</b>	0	0	0	0	0
<b>CVM</b>	45	na	1	26	72
<b>All Centers</b>	725	203	155	77	1169

\*+ 183 **BEQ** inspections (CDER specific) ⇒ total = 1352

\*\* CFSAN's BIMO Program is under reorganization

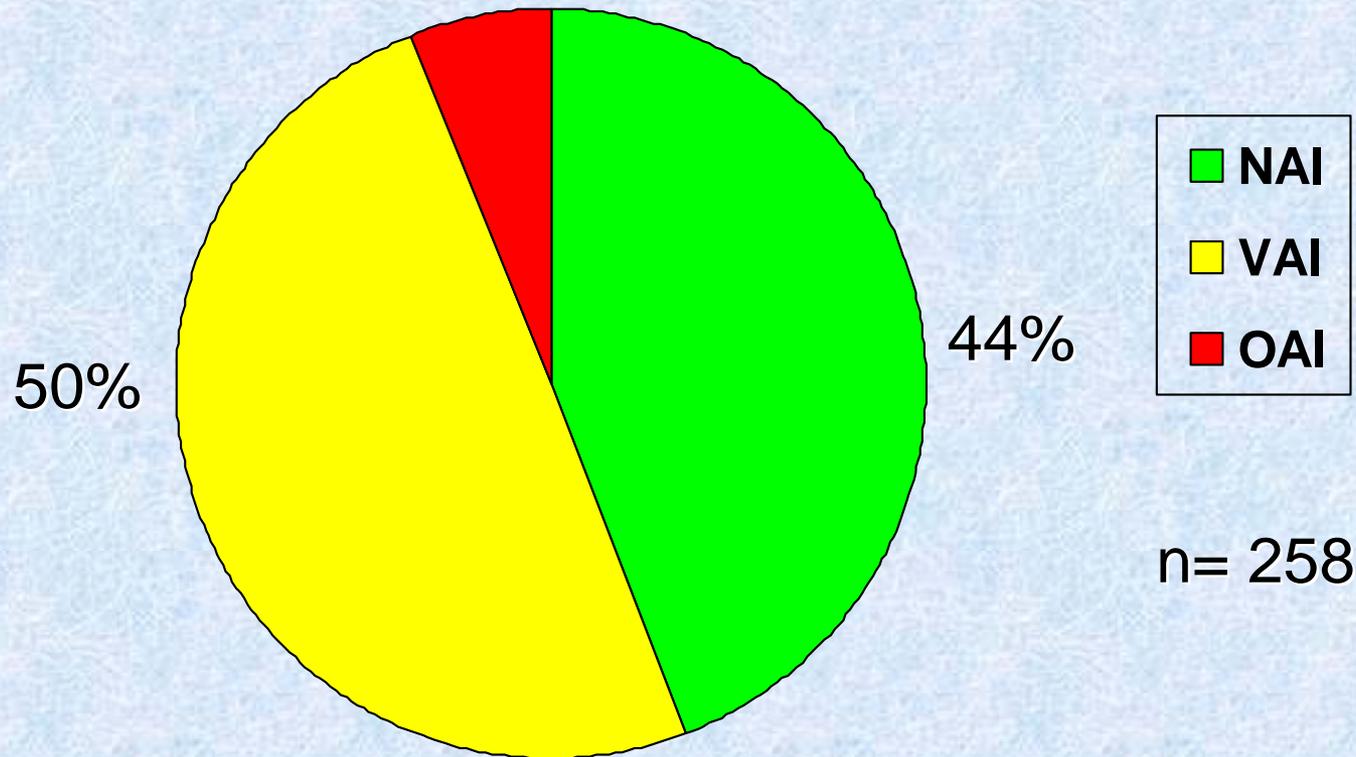
# FY'10 CI Inspections Classified\*

## All Centers



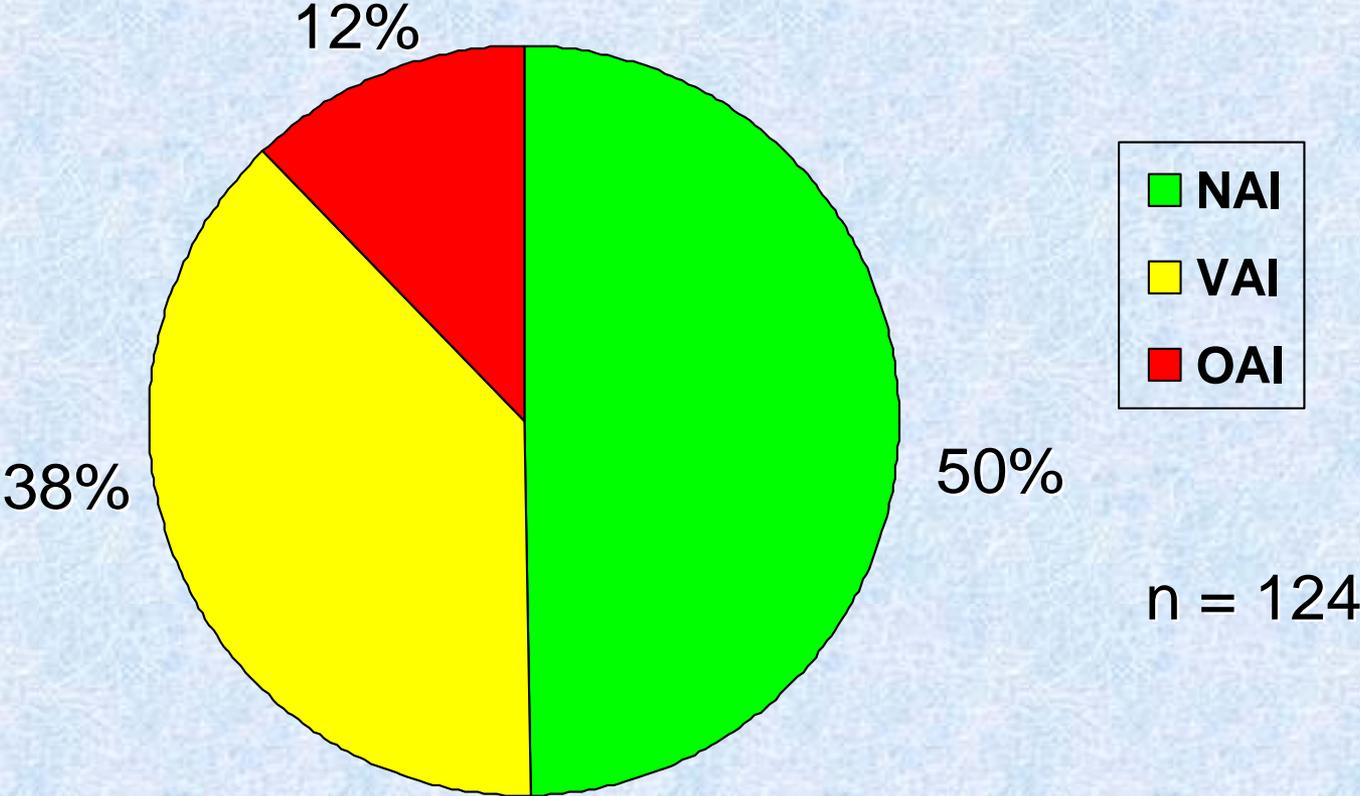
\*inspections classified in FY'10 no matter when inspection occurred

# FY'10 IRB Inspections Classified\* – All Centers



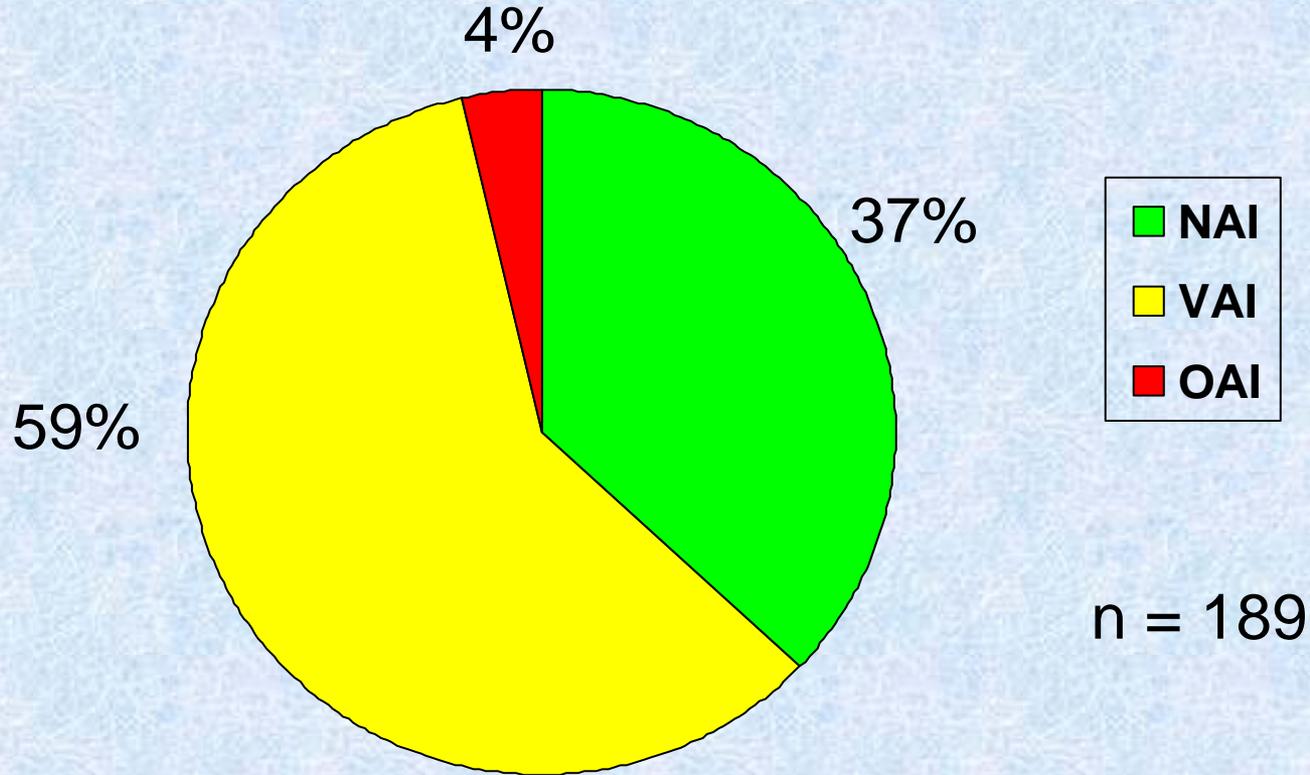
\*inspections classified in FY'10 no matter when inspection occurred

# FY'10 Sponsor/Monitor Inspections Classified\* – All Centers



\*inspections classified in FY'10 no matter when inspection occurred

# FY'10 BEQ inspections classified\*

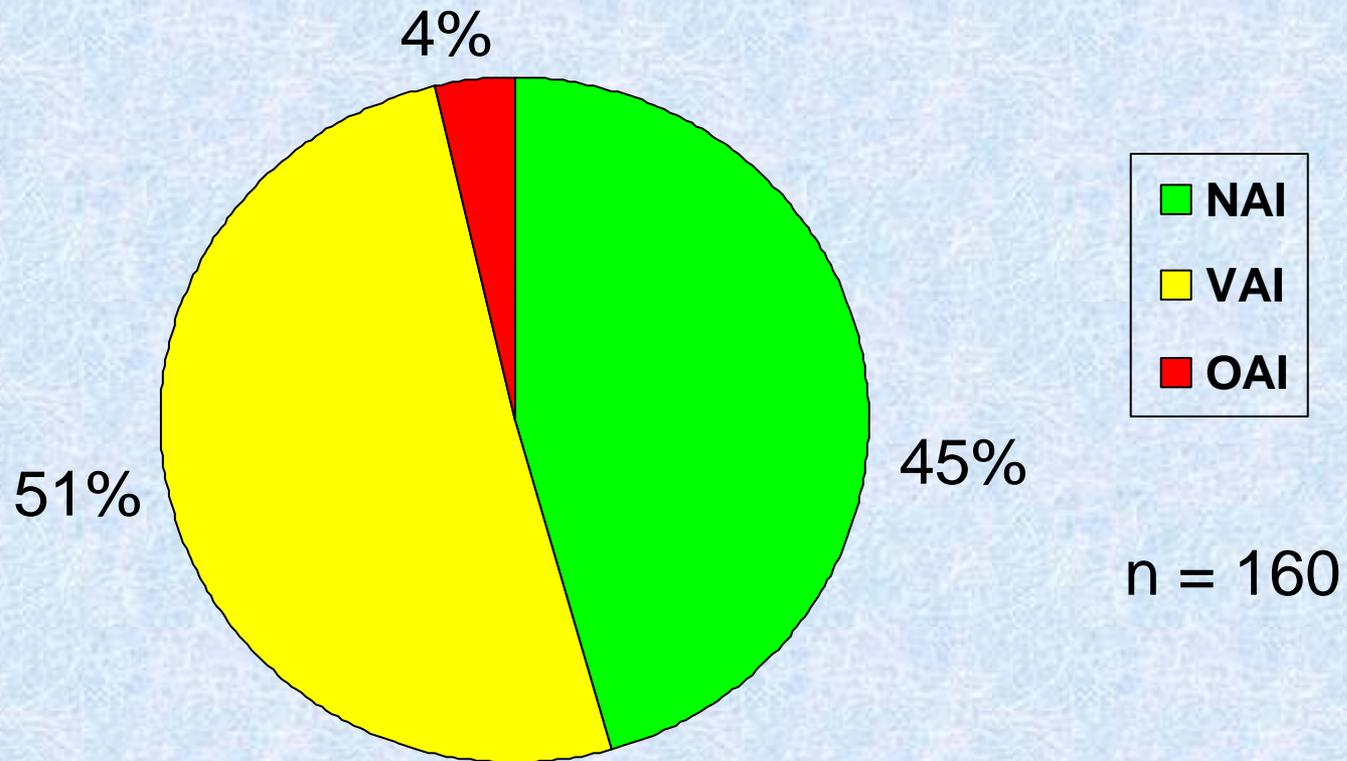


\*inspections classified in FY'10 no matter when inspection occurred

# International Inspections Completed: FY 2010

<u>Center</u>	<u>CI</u>	<u>Sponsor</u>	<u>Total</u>
<b>CBER</b>	9	1	10
<b>CDER</b>	111	0	111
<b>CDRH</b>	17	3	20
<b>CVM</b>	0	1	1
<b>Totals</b>	137	5	142

# FY'10 International CI Inspections Classified\* – All Centers



\*inspections classified in FY'10 no matter when inspection occurred

# FY'10 International Sponsor Inspections Classified\*

- CBER – 1 – NAI
- CDRH – 1 – VAI

\*inspections classified in FY'10 no matter when inspection occurred

# Resources

- GCP website –  
<http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/default.htm>
- Easier to remember routes:
  - Clinical Trials link – left column of FDA home page ([www.fda.gov](http://www.fda.gov))
  - Good Clinical Practice link in A-Z index for FDA home page

# Resources

- OGCP queries e-mail account (about 1,200 queries answered per year) – [gcp.questions@fda.hhs.gov](mailto:gcp.questions@fda.hhs.gov)
- Previous queries (2002 – 2009) – “Replies to queries...” link from GCP website (bottom of left-hand column)
- Listserve – via GCP website – notice of updates on FDA’s GCP/HSP activities

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